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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,624	09/04/2003	Philip C. Wong	JHU1690-3	7979

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,624	WONG ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11.3.03 11.19.03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The Preliminary Amendment filed 4 September 2003 has been received and entered in full.

2. The Preliminary Amendment filed 27 February 2004 has been received and entered in full.

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 13-15 and 19-23 of the instant application. The Provisional Application No. 60/244,051 is drawn to two inventions: (1) construction of a transgenic mouse and (2) in vitro screening methods to identify compounds which inhibit BACE1 and BACE2. The provisional application does not contain any support for the instant method of diagnosis or assessment of risk for a subject having an Aβ11-40/42 accumulation disease.The instant Application contains support for the instant invention in the parent Application No. 09/708,096 and thus is granted the priority date of 3 November 2000.

Information Disclosure Statement

5. The Examiner notes that the references listed on the PTO-892 and PTO-1449 in the Information Disclosure Statement filed 4 September 2004 were taken into consideration during the examination of the parent, Application No. 09/708,096 (see MPEP §609). The Examiner has taken these references into consideration in the instant Application. Applicant need not provide a

citation of these references in the instant application unless Applicant wishes for these references to be published on the face of the patent [see MPEP §2001.06(b)].

Specification

6. The disclosure is objected to because of the following informalities: mixed font "ons*et* *Alz*heimer's" (pp. 4 line 2); typo " $^{17\text{-}19}$ " (pp. 57 line 8). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim **13** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "Aβ11-40/42 peptide accumulation disease" in claim 13 is used by the claim to mean "diseases with Aβ11-40/42 peptide accumulation", while the accepted meaning is not clear. The term is indefinite because the neither specification nor the art clearly defines the term.

9. The instant invention involves measurement of Aβ in a biological sample from a subject. This may or may not be associated with a specific pathological condition such as Alzheimer's disease. For instance, Walker *et al.* (July 1994) "Labeling of cerebral amyloid in vivo with a monoclonal antibody." J Neuropathol Exp Neurol. **53**(4):377-83 teaches that aged monkeys show Aβ deposits but no outward signs or symptoms of Alzheimer's disease. Furthermore the art does not recognize "Aβ11-40/42 peptide accumulation disease" *per se* but breaks it into to categories, Aβ accumulation without a distinct pathology (as shown by Walker *et al.*) and a specific pathology such as Alzheimer's disease. The Examiner respectfully suggests claim language drawn to "Aβ11-40/42 peptide accumulation" that would cover both the general non-pathological mechanistic definition and the pathology-specific definitions.

10. Claim **13** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant refers to a "normal standard value" and then both a "normal sample" and a "standard value". The mixture of the terms renders the claim indefinite as it is not clear where the "normal sample" and "standard value" originate and as such one could not practice the method as claimed.

11. Claim **13** is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: from where the "normal sample" and "standard value" originate. The claims as instantly presented do not teach where how is determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims **13-15** and **19-23** are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 855 444 A2 (29 July 1998) Smithkline Beecham PLC (Powell *et al.*)

13. EP 0 855 444 A2 teaches a diagnostic assay comprising measuring the level of Asp2 in a biological sample to diagnosis or determine the susceptibly to Alzheimer's disease thus meeting the limitations of claims 13 and 23 (pp. 11 lines 5-35). The Examiner notes that "at risk of having" and "susceptibility" are synonymous as is readily apparent from the definition of susceptible (Dictionary.com definition included herein). In addition, EP 0 855 444 A2 teaches that increased Asp2 (also known as BACE1, see below) levels can be assessed by either mRNA via Northern blot, for example, or protein levels via immunoassay, for example, thus meeting the limitations of claims 13 and 15 (pp. 11 lines 27-33). EP 0 855 444 A2 teaches the assessment of the over-expression or abnormal levels of Asp2 (reflected both by mRNA and protein) implying a comparison to a normal (non-pathological) patient index thus meeting the limitations of claim 13 (pp. 11 lines 30-35).

14. EP 0 855 444 A2 teaches said diagnostic assay where in said biological samples are from blood, tissue biopsy, or autopsy material thus meeting the limitations of claim 14 (pp. 11 lines 10-11). The tissue biopsy and autopsy material as taught by EP 0 855 444 A2 inherently encompasses the brain as EP 0 855 444 A2 teaches that Asp2 is expressed in the brain, mRNA transcripts were identified in brain extracts using Northern Blots, and the brain (a key component of the CNS) is the site of Alzheimer's pathology thus meeting the limitations of claim 14 (pp. 2 lines 30-35).

15. EP 0 855 444 A2 teaches that the Asp2 protein level can be assessed by use of antibodies including but not limited to monoclonal, polyclonal antibodies it meets the limitations of claims 20-22 (pp. 2 lines 47-50). Since claims 20-22 are dependent from claim 19 which includes the limitation of "an agent that specifically binds to a BACE1 polypeptide", antibodies are considered to fall into this category thus EP 0 855 444 A2 meets the limitations of claim 19 (pp. 2 lines 47-50).

16. Claims **13-15** and **19-23** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,319,689 B1 (20 November 2001) Powell *et al.*

17. US '689 teaches a diagnostic assay comprising measuring the level of Asp2 in a biological sample to diagnosis or determine the susceptibly to Alzheimer's disease thus meeting the limitations of claims 13 and 23 (Col 15 lines 25-35). The Examiner notes that "at risk of having" and "susceptibility" are synonymous as is readily apparent from the definition of susceptible (Dictionary.com definition included herein). In addition, US '689 teaches that increased Asp2 (also known as BACE1, see below) levels can be assessed by either mRNA via Northern blot, for example, or protein levels via immunoassay, for example, thus meeting the

limitations of claims 13 and 15 (Col. 16 lines 1-27). US '689 teaches the assessment of the over-expression or abnormal levels of Asp2 (reflected both by mRNA and protein) implying a comparison to a normal (non-pathological) patient index thus meeting the limitations of claim 13 (Col. 15 lines 26-34).

18. US '689 teaches said diagnostic assay where in said biological samples are from blood, tissue biopsy, or autopsy material thus meeting the limitations of claim 14 (Col. 15 line 35-37). The tissue biopsy and autopsy material as taught by US '689 inherently encompasses the brain as US '689 teaches that Asp2 is expressed in the brain, mRNA transcripts were identified in brain extracts using Northern Blots, and the brain (a key component of the CNS) is the site of Alzheimer's pathology thus meeting the limitations of claim 14 (Col. 9 lines 32-37; Col. 22 lines 8-29).

19. US '689 teaches that the Asp2 protein level can be assessed by use of antibodies including but not limited to monoclonal, polyclonal antibodies it meets the limitations of claims 20-22 (Col. 2 lines 1-6). Since claims 20-22 are dependent from claim 19 which includes the limitation of "an agent that specifically binds to a BACE1 polypeptide", antibodies are considered to fall into this category thus US '689 meets the limitations of claim 19 (Col. 2 lines 1-6).

Summary

20. No claims are allowed.

21. The Examiner notes that BACE1 is a β-secretase and this enzyme has been independently identified by four different groups. As such BACE1 is also known as BACE, Asp2, Memapsin 2,

and, generically, β-secretase {see Phimister (18 January 2000) "Four companies announce discovery of β-secretase gene. Nature Biotechnology **18**(1): 16; Bennett *et al.* (7 July 2000) "Expression Analysis of BACE2 in Brain and Peripheral Tissues." Journal of Biological Chemistry **275**(27): 20647-20651; Nunan & Small (13 October 2000) "Regulation of APP cleavage by α-, β- and γ-secretases." FEBS Letters **483**(1): 6-10; Turner *et al.* (9 July 2002) "Specificity of Memapsin 1 and Its Implications on the Design of Memapsin 2 (β-Secretase) Inhibitor Selectivity." Biochemistry **41**(27): 8742-8746; Huse *et al.* (27 October 2000) "Maturation and Endosomal Targeting of β-Site Amyloid Precursor Protein-cleaving Enzyme." The Journal of Biological Chemistry **275**(43): 33729-33737}.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
January 18, 2005